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L1             0 FILE CAPLUS
L2             0 FILE MEDLINE
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L3             0 S ((HIV (3W)(REVERSE TRANSCRIPTASE)) OR NNRTI) AND 103S
L4          3448 FILE CAPLUS
L5          3903 FILE MEDLINE
     TOTAL FOR ALL FILES
L6          7351 S ((HIV (3W)(REVERSE TRANSCRIPTASE)) OR NNRTI)
L7            49 FILE CAPLUS
L8            38 FILE MEDLINE
     TOTAL FOR ALL FILES
L9            87 S ((HIV (3W)(REVERSE TRANSCRIPTASE)) OR NNRTI) AND (103)
L10           61 DUPLICATE REMOVE L9 (26 DUPLICATES REMOVED)
L11           49 S L10
L12           49 FILE CAPLUS
L13           12 S L10
L14           12 FILE MEDLINE
     TOTAL FOR ALL FILES
L15           61 S L10 NOT PATENTS/DT

     FILE 'CAPLUS' ENTERED AT 16:24:42 ON 01 DEC 2004

=> d l12 25-49 bib,abs

L12  ANSWER 25 OF 49  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   1998:298889  CAPLUS
DN   129:15939
TI   New Alkenyldiarylmethanes with Enhanced Potencies as Anti-HIV Agents Which
     Act as Non-Nucleoside Reverse Transcriptase Inhibitors
AU   Cushman, Mark; Casimiro-Garcia, Agustin; Hejchman, Elzbieta; Ruell,
     Jeffrey A.; Huang, Mingjun; Schaeffer, Catherine A.; Williamson, Karen;
     Rice, William G.; Buckheit, Robert W., Jr.
CS   Department of Medicinal Chemistry and Molecular Pharmacology School of
     Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN,
     47907, USA
SO   Journal of Medicinal Chemistry (1998), 41(12), 2076-2089
     CODEN: JMCMAR; ISSN: 0022-2623
PB   American Chemical Society
DT   Journal
LA   English
AB   Twenty-two new alkenyldiarylmethanes (ADAMs) were synthesized and
     evaluated for inhibition of HIV-1 replication.  The most potent compound
     proved to be Me 3',3''-dichloro-4',4''-dimethoxy-5',5''-
     bis(methoxycarbonyl)-6,6-diphenyl-5-hexenoate (ADAM II), which displayed
     an EC50 of 13 nM for inhibition of the cytopathic effect of HIV-1RF in
     CEM-SS cells.  ADAM II inhibited HIV-1 reverse
     transcriptase with an IC50 of 0.3 μM but was inactive as an
     inhibitor of HIV-1 attachment/fusion to cells, protease, integrase, and
     the nucleocapsid protein.  Mol. target-based and cell-based assays
     revealed that ADAM II acted biol. as a non-nucleoside reverse
     transcriptase inhibitor (NNRTI).  ADAM II inhibited replication
     of a wide variety of laboratory, clin., and clade-representative isolates of
     HIV-1 in T cell lines and cultures of peripheral blood mononuclear cells
     or monocyte/macrophages.  Mutations that conferred resistance to ADAM II
     clustered at residues 101, 103, 108, 139, 179, 181, and 188,
     which line the non-nucleoside binding pocket of HIV-1
     reverse transcriptase.  However, HIV-1 NL4-3 strain
     expressing a mutation at residue 100 of reverse transcriptase, and an
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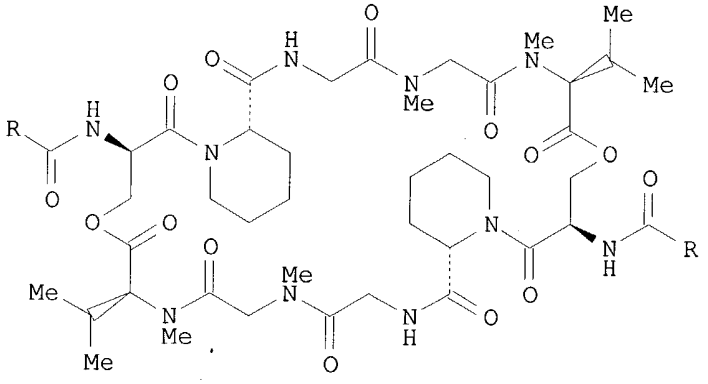
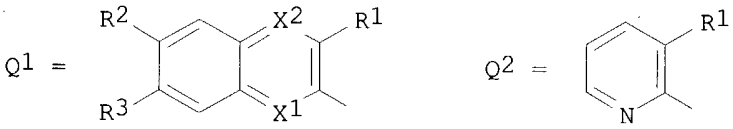
AZT-resistant virus, displayed increased sensitivity to ADAM II. Thus, ADAM II could serve as an adjunct therapy to AZT and **NNRTIs** that select for L100I resistance mutations.

RE.CNT 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 26 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:102448 CAPLUS
DN 128:192915
TI Synthesis of key sandramycin analogs: systematic examination of the intercalation chromophore
AU Boger, Dale L.; Chen, Jyun-Hung; Saionz, Kurt W.; Jin, Qing
CS Department of Chemistry and The Skaggs Institute of Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SO Bioorganic & Medicinal Chemistry (1998), 6(1), 85-102
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Science Ltd.
DT Journal
LA English
GI



I



AB The preparation and examination of sandramycin analogs I (R = Q, Q1, 1-isoquinolyl, 3-isoquinolyl; X1, X2 = CH, N; R1 = H, OH, OCH2Ph, OMe; R2 = H, MeO, Me; R3 = H, Cl) constituting a systematic study of the chromophore are detailed. Fluorescence quenching studies were used to establish binding consts. for I within calf thymus DNA, within a single high affinity bis-intercalation binding site 5'-d(GCATGC)2, and to establish the preference for sandramycin binding to 5'-d(GCXXGC)2 (XX = AT, TA, GC, CG). From the latter studies, sandramycin was found to exhibit a preference that follows the order: 5'-d(GCATGC)2 > 5'- d(GCGCGC)2, $\Delta\Delta G^\circ$ = 0.3 kcal/mol > 5'-d(GCTAGC)2, 5'-d(GCCGGC)2, $\Delta\Delta G^\circ$ = 0.6 kcal/mol although it binds with high affinity to all four deoxyoligonucleotides. The two highest affinity sequences constitute repeating 5'-PuPy motifs with each intercalation event occurring at a 5'-PyPu step. The most effective sequence constitutes the less stable duplex, contains the sterically most

accessible minor groove central to the bis-intercalation site, and the ability to accept two Gly-NH/T C2 carbonyl H-bonds identified in prior NMR studies. Similarly, the contribution of the individual structural features of the chromophore were assessed with the high affinity duplex sequence 5'-d(GCATGC)2. To a first approximation, the cytotoxic properties were found to parallel trends established in the DNA binding affinities. The exception to this generalization was I (R = Q1; X1 = N, X2 = CH, R1 = OMe, R2 = R3 = H) which lacks the sandramycin chromophore phenol. Although typically 4-10 + less potent than sandramycin against leukemia cell lines, it proved to be 1-10,000+ more potent against melanomas, carcinomas, and adenocarcinomas exhibiting IC50 values of 1 pM-10 nM placing it among the most potent agents identified to date. Addnl., the first disclosure of the **HIV**-1 **reverse transcriptase** inhibitory activity of sandramycin as well as that of its key analogs are described and define the chromophore structural features required for their exceptional potency. Two analogs I (R = Q1; X1 = X2 = N, R1-R3 = H; X1 = N, X2 = CH, R1 = OMe, R2 = R3 = H) roughly maintain the **HIV**-1 **reverse transcriptase** inhibitory potency of sandramycin but exhibit substantially diminished cytotoxic activity (102-**103**+).

RE.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 27 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:479342 CAPLUS
DN 127:95191
TI Preparation of furan- and thiophenecarbothioamide derivatives and their use as inhibitors of the replication of HIV-1 and HIV-1 mutants
IN Brouwer, Walter Gerhard; Osika, Ewa Maria; Pierce, Benjamin James
PA Uniroyal Chemical Company, Inc., USA; Uniroyal Chemical Ltd./uniroyal Chemical Ltee
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9719940	A1	19970605	WO 1996-US18394	19961115
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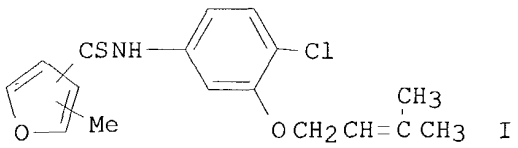
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5696151	A	19971209	US 1995-565493	19951130
	TW 448169	B	20010801	TW 1996-85113662	19961108
	ZA 9609490	A	19970602	ZA 1996-9490	19961112
	CA 2237194	AA	19970605	CA 1996-2237194	19961115
	AU 9711199	A1	19970619	AU 1997-11199	19961115
	AU 704086	B2	19990415		
	EP 874839	A1	19981104	EP 1996-942010	19961115
	EP 874839	B1	20020918		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	CN 1203596	A	19981230	CN 1996-198705	19961115
	CN 1098847	B	20030115		
	BR 9611838	A	19990309	BR 1996-11838	19961115
	JP 3027771	B2	20000404	JP 1997-520533	19961115
	JP 11504657	T2	19990427		
	AP 902	A	20001123	AP 1998-1245	19961115
	W: GM, GH, KE, LS, MW, SD, SZ, UG, ZW				
	AT 224382	E	20021015	AT 1996-942010	19961115
	PT 874839	T	20030228	PT 1996-942010	19961115
	ES 2183986	T3	20030401	ES 1996-942010	19961115
	HK 1016601	A1	20030905	HK 1999-101720	19990421

PRAI US 1995-565493 A 19951130
WO 1996-US18394 W 19961115
OS MARPAT 127:95191
GI



I

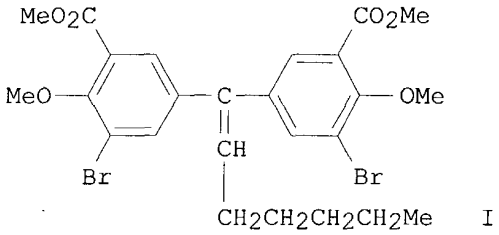
AB Compds. of formula (I), wherein X = O or S. The compds. of this invention are useful for the inhibition of the replication of human immunodeficiency virus-1 (**HIV**-1) and **reverse transcriptase** (RT) mutants thereof, in vitro and in vivo. The compds. are useful in the therapeutic or prophylactic treatment of diseases caused by HIV-1 and RT mutants thereof, such as acquired immune deficiency syndrome (AIDS). Thus, N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furancarboxamide 4, sodium bicarbonate 7.4, and Lawesson's reagent 3.6g were heated to 85°C and held at 85° for 2.5 h to give 2.6g of I (X = O). I (X = O) showed EC50 syncytium formation inhibiting values of 0.003, 0.006, 0.005, 0.005, 0.011, and 0.50 μg/mL for HIV-1 infected cells 100-Ile, **103**-Asn, 106-Ala, 138-Lys, 181-Cys, and 188-Leu, resp.

L12 ANSWER 28 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:263284 CAPLUS
DN 126:324999
TI Unique features in the structure of the complex between **HIV**-1 **reverse transcriptase** and the bis(heteroaryl)piperazine (BHAP) U-90152 explain resistance mutations for this nonnucleoside inhibitor
AU Esnouf, Robert M.; Ren, Jingshan; Hopkins, Andrew L.; Ross, Carl K.; Jones, E. Yvonne; Stammers, David K.; Stuart, David I.
CS Lab. Mol. Biophysics, Oxford, OX1 3QU, UK
SO Proceedings of the National Academy of Sciences of the United States of America (1997), 94(8), 3984-3989
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB The viral reverse transcriptase (RT) provides an attractive target in the search for anti-HIV therapies. The nonnucleoside inhibitors (NNIs) are a diverse set of compds. (usually HIV-1 specific) that function by distorting the polymerase active site upon binding in a nearby pocket. Despite being potent and of generally low toxicity, their clin. use has been limited by rapid selection for resistant viral populations. The 2.65-Å resolution structure of the complex between HIV-1 RT and the bis(heteroaryl)piperazine (BHAP) NNI, 1-(5-methanesulfonamido-1H-indol-2-yl-carbonyl)-4-[3-(1-methyl-ethylamino)pyridinyl] piperazine (U-90152), reveals the inhibitor conformation and bound water mols. The bulky U-90152 mol. occupies the same pocket as other NNIs, but the complex is stabilized quite differently, in particular by hydrogen bonding to the main chain of Lys-**103** and extensive hydrophobic contacts with Pro-236. These interactions rationalize observed resistance mutations, notably Pro-236-Leu, which occurs characteristically for BHAPs. When bound, part of U-90152 protrudes into the solvent creating a channel between Pro-236 and the polypeptide segments 225-226 and 105-106, giving the first clear evidence of the entry mode for NNIs. The structure allows prediction of binding modes for related inhibitors [(altrylamino)piperidine-BHAPs] and suggests changes to U-90152, such as

the addition of a 6 amino group to the pyridine ring, which may make binding more resilient to mutations in the RT. The observation of novel hydrogen bonding to the protein main chain may provide lessons for the improvement of quite different inhibitors.

RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 29 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:422513 CAPLUS
DN 125:104565
TI Synthesis and biological evaluation of certain alkenyldiarylmethanes as anti-HIV-1 agents which act as non-nucleoside reverse transcriptase inhibitors
AU Cushman, Mark; Golebiewski, W. Marek; Graham, Lisa; Turpin, Jim A.; Rice, William G.; Fliakas-Boltz, Valerie; Buckheit, Robert W., Jr.
CS School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN, 47907, USA
SO Journal of Medicinal Chemistry (1996), 39(16), 3217-3227
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
GI



I

AB Several novel alkenyldiarylmethane (ADAM) non-nucleoside **HIV**-1 **reverse transcriptase** inhibitors were synthesized. The most potent of these proved to be 3',3''-dibromo-4',4''-dimethoxy-5',5''-bis(methoxycarbonyl)-1,1-diphenyl-1-heptene (I). ADAM I inhibited the cytopathic effect of HIV-1 in CEM cell culture with an EC50 value of 7.1 μM and was active against an array of laboratory strains of HIV-1 in CEM-SS and MT-4 cells, but was inactive as an inhibitor of HIV-2. In common with the other known non-nucleoside reverse transcriptase inhibitors, ADAM I was an effective inhibitor of **HIV**-1 **reverse transcriptase** (IC50 1 μM) with poly(rC)·oligo(dG), but not with poly(rA)·oligo(dG), as the template primer. ADAM I was inactive against **HIV**-1 **reverse transcriptases** containing non-nucleoside reverse transcriptase inhibitor resistance mutations at residues 101, 106, 108, 139, 181, 188, and 236, while it remained active against enzymes with mutations at residues 74, 98, 100, **103**, and at **103**/181. An AZT-resistant virus having four mutations in reverse transcriptase was more sensitive to inhibition by ADAM I than the wild-type HIV-1. In addition, ADAM I displayed synergistic activity with AZT, but lacked synergy with ddI. ADAM I or a structurally related analog may therefore be useful as an antiviral agent in combination with AZT or with other **NNRTIs** that are made ineffective by mutations at residues which do not confer resistance to ADAM I.

L12 ANSWER 30 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:967831 CAPLUS
DN 124:219374
TI Structure-activity and cross-resistance evaluations of a series of human immunodeficiency virus type 1-specific compounds related to oxathiin

carboxanilide
AU Buckheit, Robert W., Jr.; Kinjerski, Tracy L.; Fliakas-Boltz, Valerie; Russell, Julie D.; Stup, Tracy L.; Pallansch, Luke A.; Brouwer, Walter G.; Dao, Dong C.; Harrison, W. Ashley; et al.
CS Virol. Res. Group, Southern Res. Inst.-Frederick Res. Cent., Frederick, MD, 21701, USA
SO Antimicrobial Agents and Chemotherapy (1995), 39(12), 2718-27
CODEN: AMACCQ; ISSN: 0066-4804
PB American Society for Microbiology
DT Journal
LA English
AB A series of compds. related to the nonnucleoside reverse transcriptase (RT) inhibitor (**NNRTI**) oxathiin carboxanilide (UC84) were evaluated for activity against the human immunodeficiency virus (HIV) to determine structural requirements for anti-HIV activity. Twenty-seven compds. representative of the more than 400 Uniroyal Chemical Company (UC) compds. were evaluated for structure-activity relationships. Several of the compds. evaluated were highly active, with 50% effective concns. in the nanomolar range and therapeutic indexes of >1,000. Highly synergistic anti-HIV activity was observed for each compound when used in combination with 3'-azido-3'-deoxythymidine; additive to slightly synergistic interactions were observed with the compds. used in combination with dideoxycytidine. In combination with the **NNRTI** costatolide, only UC38 synergistically inhibited HIV type 1. Residues in the RT which, when mutated, impart resistance to the carboxyanilide compds. were defined by evaluation of the UC compds. against a panel of **NNRTI**-resistant virus isolates selected in cell culture, against virus variants with site-directed mutations, and against RTs containing defined single amino acid changes. The mutations included changes in RT amino acids 100, 101, **103**, 106, 108, and 181. The results with isolates selected in cell culture indicate that the carboxanilide compds. interact with the RT at two vulnerable sites, selecting UC-resistant virus isolates with the Y-to-C mutation at position 181 (Y181C) or the L100I substitution. A resistant virus isolate containing both Y181C and K101E amino acid changes and another with both Y181C and V106A mutations were isolated. In combination with calanolide A, an **NNRTI** which retains activity against virus isolates with the single Y181C mutation, UC10 rapidly selected a virus isolate with the K103N mutation. The merits of selecting potential candidate anti-HIV agents to be used in rational combination drug design as part of an armamentarium of highly active anti-HIV compds. are discussed.

L12 ANSWER 31 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:642292 CAPLUS
DN 123:74260
TI Resistance to 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine derivatives is generated by mutations at multiple sites in the **HIV**-1 **reverse transcriptase**
AU Buckheit, Robert W., Jr.; Fliakas-Boltz, VAlerie; Yeagy-Bargo, Sharon; Weislow, Owen; Mayers, Douglas L.; Boyer, Paul L.; Hughes, Stephen H.; Pan, Bai-Chuan; Chu, Shih-Hsi; et al.
CS Virology Research Group, Southern Research Institute-Frederick Research Center, Frederick, MD, 21701, USA
SO Virology (1995), 210(1), 186-93
CODEN: VIRLAX; ISSN: 0042-6822
PB Academic
DT Journal
LA English
AB Virus isolates resistant to 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) and a highly potent HEPT derivative, [1-benzyloxymethyl-5-ethyl-6-(α-pyridylthio)uracil] (NSC 648400, E-BPTU), were selected in cell culture. Cross-resistance evaluation indicated that the two drug-resistant virus isolates were phenotypically distinct from one another although each of the virus isolates was

resistant to both of the HEPT derivs. The virus isolate resistant to NSC 648400 had a single amino acid change in the reverse transcriptase (Y181C) which resulted in cross-resistance to all of the nonnucleoside reverse transcriptase inhibitors evaluated, with the exception of calanolide A. The NSC 648400-resistant virus isolate exhibited 15-fold enhanced sensitivity to calanolide A. The virus isolate selected in the presence of HEPT exhibited a single amino acid change (P236L) which was not cross-resistant to other nonnucleoside RT inhibitors tested with the exception of the two HEPT derivs. This HEPT-resistant virus isolate exhibited enhanced sensitivity (5-to 10-fold) to thiazolobenzimidazole. We have used both virus isolates with defined single amino acid changes in the RT and bacterially expressed RTs with site-directed amino acid substitutions to test the effects of a wide variety of mutations on the activity of NSC 648400. Single mutations at amino acids 101, **103**, 106, 181, or 236 yielded virus with high resistance (>20-fold) to NSC 648400, while lower levels of resistance were seen with mutations at amino acids 98, 100, or 108. These results suggest that several changes in the conformation of the nonnucleoside inhibitor binding site of the **HIV**-1 **reverse transcriptase** can affect the inhibitory activity of the HEPT class of compds.

L12 ANSWER 32 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:617308 CAPLUS
DN 123:74255
TI Suppression of the breakthrough of human immunodeficiency virus type 1 (HIV-1) in cell culture by thiocarboxanilide derivatives when used individually or in combination with other HIV-1-specific inhibitors (i.e., TSAO derivatives)
AU Balzarini, J.; Perez-Perez, M.-J.; Velazquez, S.; San-Felix, A.; Camarasa, M.-J.; De Clercq, E.; Karlsson, A.
CS Rega Institute Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.
SO Proceedings of the National Academy of Sciences of the United States of America (1995), 92(12), 5470-4
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB Five structurally related thiophene and furane analogs of the oxathiin carboxanilide derivative NSC 615985 (UC84) (designated UC10, UC68, UC81, UC42, and UC16) were identified as potent inhibitors of HIV-1 replication in cell culture and **HIV**-1 **reverse transcriptase** activity. These compds. were markedly active against a series of mutant HIV-1 strains, containing the Leu-100 → Ile, Val-106 → Ala, Glu-138 → Lys, or Tyr-181 → Cys mutations in their reverse transcriptase. However, the thiocarboxanilide derivs. selected for mutations at amino acid positions 100 (Leu → Ile), 101 (Lys → Ile/Glu), **103** (Lys → Thr/Asp) and 141 (Gly → Glu) in the **HIV**-1 **reverse transcriptase**. The compds. completely suppressed HIV-1 replication and prevented the emergence of resistant virus strains when used at 1.3-6.6 μM-i.e., 10- to 25-fold lower than the concentration required for nevirapine and bis(heteroaryl)piperazine (BHAP) U90152 to do so. If UC42 was combined with the [2',5'-bis-O-(tert-butyldimethylsilyl)-3'-spiro-5''-(4''-amino-1'',2''-oxathiole-2'',2''-dioxide)]-β-D-pentofuranosyl (TSAO) derivative of N3-methylthymine (TSAO-m3T), virus breakthrough could be prevented for a much longer time, and at much lower concns., than if the compds. were used individually. Virus breakthrough could be suppressed for even longer, and at lower drug concns., if BHAP was added to the combination of UC42 with TSAO-m3T, which points to the feasibility of two- or three-drug combinations in preventing virus breakthrough and resistance development.

L12 ANSWER 33 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1995:460370 CAPLUS
DN 122:229855
TI Resistance of human immunodeficiency virus type 1 (HIV-1) to non-nucleoside **HIV**-1-specific **reverse transcriptase** inhibitors
AU De Clercq, E.
CS Rega Institute Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.
SO International Journal of Immunotherapy (1994), 10(4), 145-58
CODEN: IJIMET; ISSN: 0255-9625
PB Bioscience Ediprint
DT Journal; General Review
LA English
AB A review, with 63 refs. Various non-nucleoside reverse transcriptase inhibitors (**NNRTIs**) have been reported to specifically inhibit HIV-1: viz. tetrahydroimidazobenzodiazepinone (TIBO), hydroxyethoxymethylphenylthiothymine (HEPT), dipyridodiazepinone (i.e. nevirapine), pyridinone, bis(heteroaryl)piperazine (BHAP), tert-butyldimethylsilylspiroaminooxathiole-dioxide (TSAO), α-anilinophenylacetamide (α-APA) and quinoxaline derivs. The most potent among the TIBO, HEPT and α-APA derivs. have been found to inhibit HIV-1 replication at nanomolar concns. that are 100,000-fold lower than the cytotoxic concns. These compds. therefore offer great potential for the treatment of HIV-1 infections. However, the virus may rapidly develop resistance to these drugs. The mutations conferring resistance have been mapped at the reverse transcriptase positions 100 (Leu → Ile), **103** (Lys → Asn), 106 (Val → Ala), 108 (Val → Ile), 138 (Glu → Lys), 179 (Val → Asp), 181 (Tyr → Cys → Ile), 188 (Tyr → Cys/His), 190 (Gly → Glu), 230 (Met → Ile) and 236 (Pro → Leu). However, these mutations do not necessarily lead to cross-resistance among the various **NNRTIs** and, in some cases, they have proved to be mutually suppressive. Several strategies can be envisaged to circumvent or prevent the resistance problem: (i) switching from one **NNRTI** (to which the virus has developed resistance) to another (to which it has not developed resistance); (ii) combinations of different **NNRTIs** that do not confer cross-resistance, or even counteract development or resistance to one another; (iii) using from the start sufficiently high ("knocking out") concns. to completely shut off virus replication and prevent resistance from emerging; and (i.v.) by combining strategies (ii) and (iii), using from the start combinations of different drugs to achieve virus "knock out" at even lower concns.

L12 ANSWER 34 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:445027 CAPLUS
DN 122:230221
TI Isolation and characterization of human immunodeficiency virus type-1 mutants resistant to the non-nucleotide reverse transcriptase inhibitor MKC-442
AU Seki, M.; Sadakata, Y.; Yuasa, S.; Baba, M.
CS Laboratory of Bioscience, Mitsubishi Kasei Corp., Yokohama, 227, Japan
SO Antiviral Chemistry & Chemotherapy (1995), 6(2), 73-9
CODEN: ACCHEH; ISSN: 0956-3202
PB Blackwell
DT Journal
LA English
AB MKC-442, 6-benzyl-1-ethoxymethyl-5-isopropyluracil (I-EBU), is a potent and selective non-nucleoside inhibitor of human immunodeficiency virus type-1 (**HIV**-1) **reverse transcriptase** (RT). Nevirapine, another non-nucleoside RT inhibitor (**NNRTI**), is associated with rapid emergence of drug-resistant variants during in vitro passages of HIV-1. The emergence of resistant viruses to MKC-442 or nevirapine was examined in vitro. MT-4 cells infected with a clin. isolate (HE) of HIV-1 were cultivated in medium containing excess concns. of these

drugs, and the drug susceptibilities of the breakthrough viruses recovered from the medium were measured. Although nevirapine lost its antiviral activity after six passages, a delay in the emergence of fully resistant viruses was observed for MKC-442. Two resistant clones for each drug were isolated and nucleotide sequences within the RT region were analyzed. An amino acid substitution at position 181 (Tyr to Cys) was found, with addnl. substitutions at positions **103** (Lys to Arg) and 108 (Val to Ile) in the MKC-442-resistant viruses. These clones showed various susceptibilities to MKC-442, and cross-resistance to other **NNRTIs** but not to AZT. These results suggest that the major binding site of MKC-442 on the HIV-1 RT is the tyrosine residue common to these **NNRTIs**, and that drug resistance to **NNRTIs** is dependent on both the quality and the quantity of mutations within the HIV-1 RT gene.

L12 ANSWER 35 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:218604 CAPLUS
DN 122:45772
TI Resistance pattern of human immunodeficiency virus type 1 reverse transcriptase to quinoxaline S-2720
AU Balzarini, Jan; Karlsson, Anna; Meichsner, Christoph; Paessens, Arno; Riess, Guenther; De Clercq, Erik; Kleim, Joerg-Peter
CS Rega Institute for Medical Research, Katholieke Universiteit Leuven, Lueven, B-3000, Belg.
SO Journal of Virology (1994), 68(12), 7986-92
CODEN: JOVIAM; ISSN: 0022-538X
PB American Society for Microbiology
DT Journal
LA English
AB The human immunodeficiency virus type 1 (**HIV**-1)-specific **reverse transcriptase** (RT) inhibitor quinoxaline S-2720 showed a more-potent inhibitory effect on HIV-1-induced cytopathicity in CEM cells than either nevirapine, pyridinone L-697, 661, bis-heteroarylpiperazine (BHAP) U-88204, TSAO, or R82913. The quinoxaline derivative was also markedly more inhibitory to the mutant HIV-1 strains containing in their RT Ile-100, Asn-**103**, Ala-106, Lys-138, Cys-181, or His-188 substitutions than were the other HIV-1-specific RT inhibitors. Moreover, quinoxaline S-2720 totally prevented HIV-1 infection and emergence of drug-resistant mutant virus strains in CEM cell cultures at concns. (i.e., 0.35 μM) that are 10- to 25-fold lower than those required for BHAP U-88204 and nevirapine to knock out the virus. Also, the concentration-response curve for S-2720 was markedly steeper than for BHAP and nevirapine, as reflected by the ratio of the 95% to the 50% antivirally effective concentration Lower concns. of quinoxaline dominantly lead to the appearance of the Ala-106 RT mutation, causing low-level resistance to the compound At higher quinoxaline concns., the Glu-190 RT and/or the Cys-181 RT mutation is added to the Ala-106 mutation, whereas at the highest quinoxaline concns., the Ala-106 mutation tends to disappear from the virus pool, leaving the Glu-190 RT and Cys-181 RT mutations as the only mutations, conferring high-level resistance to the compound

L12 ANSWER 36 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:597528 CAPLUS
DN 121:197528
TI Misincorporation and mispaired primer extension by human immunodeficiency virus reverse transcriptase
AU Zinnen, Shawn; Hsieh, Jen-Chih; Modrich, Paul
CS Department of Biochemistry, Duke University Medical Center, Durham, NC, 27710, USA
SO Journal of Biological Chemistry (1994), 269(39), 24195-202
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English

AB Pre-steady-state methods were used to study the fidelity of human immunodeficiency virus reverse transcriptase. Fidelity of DNA-directed DNA synthesis can be attributed to a 1-2 order of magnitude reduction in affinity for noncomplementary dNTPs, and a 1 to 4 order of magnitude reduction in the rate of the conformational change that limits the rate of nucleotide addition Affinities of reverse transcriptase for paired or mispaired primer termini are similar. Discrimination against a mispaired primer is due to reduction in affinity for the next dNTP and reduction in rate of extension. Extension of mispaired termini proceeds a 20-700-fold faster than the rate of dissociation of reverse transcriptase from the primer-template and is 2-3 orders of magnitude more frequent than nucleotide misincorporation. The rate-limiting step for extension of a mispaired terminus occurs at the conformational change or chemical step, depending on the nature of the mispair. Presence of a mismatch at the 3' penultimate position reduces pyrophosphorolysis of the primer by a factor of **103**, indicating that mispairs 5' to the site of chemical can also affect catalysis.

L12 ANSWER 37 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:594686 CAPLUS
DN 121:194686
TI Non-nucleoside reverse transcriptase inhibitors (**NNRTIs**)
AU De Clercq, Erik
CS Rega Inst. Med. Res., Kathol. Univ. Leuven, Louvain, B-3000, Belg.
SO Expert Opinion on Investigational Drugs (1994), 3(3), 253-71
CODEN: EOIDER; ISSN: 0967-8298
DT Journal; General Review
LA English
AB A review with 98 refs. Various non-nucleoside reverse transcriptase inhibitors (**NNRTIs**) have been reported to specifically inhibit human immunodeficiency virus type 1 (HIV-1): for example, tetrahydroimidazobenzodiazepinone (TIBO), hydroxyethoxymethylphenylthiothymine (HEPT), dipyridodiazepinone (i.e. nevirapine), pyridinone, bis(heteroaryl)piperazine (BHAP), tert-butyldimethylsilylspiroaminooxathioledioxide (TSAO), α-anilinophenylacetamide (α-APA) and quinoxaline derivs. These compds. interact allosterically (i.e. non-competitively with respect to the natural substrate (dNTPs)) with a specific non-substrate binding site 'pocket' of the **HIV-1 reverse transcriptase** (RT). The most potent **NNRTIs** have been found to inhibit HIV-1 replication at nanomolar concns. These compds. therefore offer great potential for the treatment of HIV-1 infections. Yet, the virus may rapidly develop resistance to these drugs. The mutations conferring resistance have been mapped at the RT positions 100 (Leu → Ile), **103** (Lys → Asn), 106 (Val → Ala), 108 (Val → Ile), 138 (Glu → Lys), 179 (Val → Asp), 181 (Tyr → Cys), 188 (Tyr → Cys/His), 190 (Gly → Glu) and 236 (Pro → Leu). However, these mutations do not necessarily lead to cross-resistance among the various **NNRTIs**, and, in some cases, they have proved to be mutually suppressive. Several strategies could be envisaged to circumvent or prevent the resistance problem: switching from one **NNRTI** (to which the virus has developed resistance) to another (to which the virus has not developed resistance); combining different RT inhibitors that do not confer cross-resistance, or that may, in fact, even counteract development of resistance to one another; and, using sufficiently high ('knocking-out') concns. of the **NNRTIs** from the start, to completely shut down virus replication and prevent resistance from emerging. **NNRTIs** differ in several aspects from the 2',3'-dideoxynucleoside (ddN) type of RT inhibitors. An obvious strategy to be further pursued in clin. trials is based upon the combination of **NNRTIs** with ddNs, as such combinations may offer synergistic anti-HIV activity, while reducing the risk or rate of resistance development.

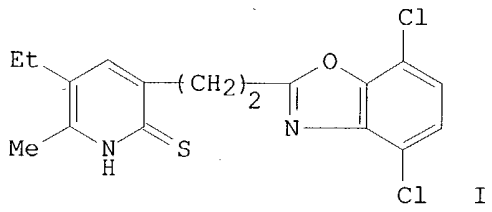
L12 ANSWER 38 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:289482 CAPLUS
DN 120:289482
TI Viral resistance to the thiazolo-iso-indolinones, a new class of nonnucleoside inhibitors of human immunodeficiency virus type 1 reverse transcriptase
AU Maass, Gerhard; Immendoerfer, Ulrike; Koenig, Bernhard; Leser, Ulrike; Mueller, Barbara; Goody, Roger; Pfaff, Eberhard
CS Bundesforschungsanst. Viruskrankheiten Tiere, Tuebingen, D-7400, Germany
SO Antimicrobial Agents and Chemotherapy (1993), 37(12), 2612-17
CODEN: AMACCQ; ISSN: 0066-4804
DT Journal
LA English
AB Thiazolo-iso-indolinone derivs. with high specificity toward the reverse transcriptase (RT) of human immunodeficiency virus type 1 (HIV-1) were identified. The most potent compound, BM +51.0836, inhibited HIV-1 RT at a 50% inhibitory concentration of 90 nM in vitro. In cell culture assays, similar 50% inhibitory concns. were obtained with high specificity for HIV-1. These substances were equally active against a zidovudine-resistant isolate. No antiviral effect was observed with an HIV-2 isolate. HIV-1 isolates resistant to the thiazolo-iso-indolinones were generated in cell culture, and the nucleotide sequences of the resp. RT genes were analyzed subsequently. Comparison of the deduced amino acid sequences with the wild-type sequence showed an amino acid change at position 181 (Tyr to Cys). Substitutions of amino acid Lys-101 and Lys-**103** as well as Tyr-181 and/or Tyr-188 by site-directed mutagenesis led to resistance against the thiazolo-iso-indolinones. A chimeric HIV-2 RT, substituted with amino acids at positions 179 to 190 from HIV-1, acquired only partial susceptibility to BM +51.0836.

L12 ANSWER 39 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:616816 CAPLUS
DN 119:216816
TI Treatment of human immunodeficiency virus type 1 (HIV-1)-infected cells with combinations of HIV-1-specific inhibitors results in a different resistance pattern than does treatment with single-drug therapy
AU Balzarini, Jan; Karlsson, Anna; Perez-Perez, Maria Jesus; Camarasa, Maria Jose; Tarpley, W. Gary; De Clercq, Erik
CS Rega Inst. Med. Res., Kathol. Univ. Leuven, Louvain, B-3000, Belg.
SO Journal of Virology (1993), 67(9), 5353-9
CODEN: JOVIAM; ISSN: 0022-538X
DT Journal
LA English
AB HIV-1-infected CEM cells were treated by the HIV-1-specific inhibitors bis-heteroarylpiperazine (BHAP), 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepinylsilyl)-β-D-ribofuranosyl]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole-2'',2''-dioxide) (TSAO-m3T), as single agents or in combination, at escalating concns. When used individually, the compds. led to the emergence of drug-resistant virus strains within two to five subcultivations. The resulting strains were designated HIV-1/BHAP, HIV-1/TIBO, HIV-1/Nev, and HIV-1/TSAO-m3T, resp. The mutant viruses showed the following amino acid substitutions in their reverse transcriptase (RT): Leu-100 → Ile for HIV-1/BHAP; Lys-**103** → Asn for HIV-1/TIBO; Val-106 → Ala for HIV-1/Nev; and Glu-138 → Lys for HIV-1/TSAO-m3T. Both the Tyr-181 → Cys and Val-106 → Ala mutations were found in another mutant emerging following treatment with nevirapine at escalating concns. The BHAP-resistant virus remained fully sensitive to the inhibitory effects of nevirapine and TSAO-m3T, whereas the TSAO-m3T-resistant virus remained fully sensitive to the inhibitory effects of nevirapine and BHAP. When different pairs of nonnucleoside RT inhibitors (i.e., BHAP plus TSAO-m3T, nevirapine plus TSAO-m3T, TIBO plus TSAO-m3T, nevirapine plus TIBO, and

BHAP plus nevirapine) were used, resistant virus emerged as fast as with single-drug therapy. In all cases the Tyr-181 → Cys mutation appeared; the virus showed markedly reduced sensitivity to all HIV-1-specific inhibitors but retained sensitivity to 2',3'-dideoxynucleoside analogs such as zidovudine, ddC, and ddI. The authors' findings argue against simultaneous combination of two different nonnucleoside RT inhibitors that are unable to inhibit HIV-1 mutant strains containing the Tyr-181 → Cys mutation when administered as single drugs.

L12 ANSWER 40 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:508440 CAPLUS
DN 119:108440
TI A mutation in reverse transcriptase of bis(heteroaryl)piperazine-resistant human immunodeficiency virus type 1 that confers increased sensitivity to other nonnucleoside inhibitors
AU Dueweke, Thomas J.; Pushkarskaya, Tatyana; Poppe, Susan M.; Swaney, Steven M.; Zhao, Jia Q.; Chen, Irvin S. Y.; Stevenson, Mario; Tarpley, W. Gary
CS Cancer Infect. Dis. Res., Upjohn Lab., Kalamazoo, MI, 49001, USA
SO Proceedings of the National Academy of Sciences of the United States of America (1993), 90(10), 4713-17
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB Several nonnucleotide inhibitors of human immunodeficiency virus type 1 (**HIV**-1) **reverse transcriptase** (RT) have been described, including nevirapine, thiobenzimidazolone (TIBO) derivs., pyridinone derivs. such as L-697,661, and bis(heteroaryl)piperazines (BHAPs). HIV-1 resistant to L-697,661 or nevirapine emerges rapidly in infected patients treated with these drugs, and the resistance is caused primarily by substitutions at amino acids 181 and **103** of RT that also confer cross-resistance to the other nonnucleoside inhibitors. Two BHAP-resistant HIV-1 variants that differ from this pattern of cross-resistance are described. In both variants, the HIV-1 resistance to BHAP RT inhibitors was caused by a RT mutation with a proline-to-leucine substitution at amino acid 236 (P236L). Rather than conferring cross-resistance to other RT inhibitors, this substitution sensitized RT 7-10-fold to nevirapine, TIBO R-82913, and L-697,661 without influencing the sensitivity to nucleoside analog RT inhibitors. The sensitization caused by P236L was also observed in cell culture infected with BHAP-resistant HIV-1. The effects of the P236L RT substitution suggest that emergence of BHAP-resistant viruses in vivo could produce viral populations sensitized to inhibition by the nonnucleoside RT inhibitors.

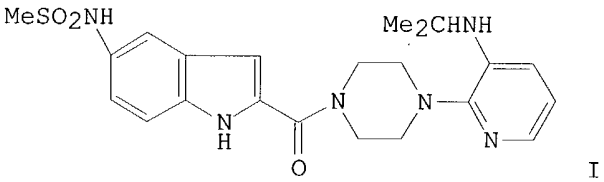
L12 ANSWER 41 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:485478 CAPLUS
DN 119:85478
TI A nonnucleoside reverse transcriptase inhibitor active on human immunodeficiency virus type 1 isolates resistant to related inhibitors
AU Goldman, Mark E.; O'Brien, Julie A.; Ruffing, Thomas L.; Schleif, William A.; Sardana, Vinod V.; Byrnes, Vera W.; Condra, Jon H.; Hoffman, Jacob M.; Emini, Emilio A.
CS Dep. New Lead Pharmacol., Merck Res. Lab., West Point, PA, 19486, USA
SO Antimicrobial Agents and Chemotherapy (1993), 37(5), 947-9
CODEN: AMACCQ; ISSN: 0066-4804
DT Journal
LA English
GI



I

AB Pyridinone derivs. are potent and specific inhibitors of human immunodeficiency virus type 1 (**HIV**-1) **reverse transcriptase** (RT) and HIV-1 replication in cell culture. However, the potential clin. usefulness of these compds. as monotherapeutic agents may be limited by the selection of inhibitor-resistant viral variants. Resistance in cell culture is due primarily to mutational alterations at RT amino acid residues **103** and 181. A recombinant HIV-1 RT containing both of these mutations was used to screen a panel of pyridinone analogs for inhibitory activity. L-696,229 and L-697,661, pyridinones currently undergoing clin. evaluation, were more than 4,000-fold weaker against the mutant enzyme than against the wild-type enzyme. In contrast, one derivative of L-696,229, L-702,019 (I), showed only three-fold against the two enzymes. I was also a potent inhibitor of the replication of mutant HIV-1 containing the individual mutations at amino acid **103** or 181 as well as of clin. isolates resistant to L-697,661 and L-696,229. Isolation and anal. of resistant viral variants in cell culture showed that signal resistance to I could be engendered only by multiple amino acid substitutions in RT. Accordingly, these studies demonstrated the potential of identifying second-generation specific HIV-1 RT inhibitors that can overcome the viral resistance selected by the first generation of inhibitors.

L12 ANSWER 42 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:462485 CAPLUS
DN 119:62485
TI U-90152, a potent inhibitor of human immunodeficiency virus type 1 replication
AU Dueweke, Thomas J.; Poppe, Susan M.; Romero, Donna L.; Swaney, Steven M.; So, Antero G.; Downey, Kathleen M.; Althaus, Irene W.; Reusser, Fritz; Busso, Mariano; et al.
CS Upjohn Lab., Kalamazoo, MI, 49001-0199, USA
SO Antimicrobial Agents and Chemotherapy (1993), 37(5), 1127-31
CODEN: AMACCQ; ISSN: 0066-4804
DT Journal
LA English
GI



I

AB Bisheteroarylpiperazines are potent inhibitors of human immunodeficiency virus type 1 (**HIV**-1) **reverse transcriptase** (RT). A novel bisheteroarylpiperazine, U-90152 (I), is described which inhibited recombinant HIV-1 RT at a 50% inhibitory concentration (IC50) of 0.26 μM (compared with IC50s of >440 μM for DNA polymerases α and δ). U-90152 blocked the replication in peripheral blood lymphocytes of 25 primary HIV-1 isolates, including variants that were highly

resistant to 3'-azido-2',3'-dideoxythymidine (AZT) or 2',3'-dideoxyinosine, with a mean 50% ED of 0.066 ± 0.137 μM. U-90152 had low cellular cytotoxicity, causing less than 8% reduction in peripheral blood lymphocyte viability at 100 μM. In expts. assessing inhibition of the spread of HIV-1IIIB in cell cultures, U-90152 was much more effective than AZT. When approx. 500 HIV-1IIIB-infected MT-4 cells were mixed 1:1,000 with uninfected cells, 3 μM AZT delayed the evidence of rapid viral growth for 7 days. In contrast, 3 μM U-90152 totally prevented the spread of HIV-1, and death and/or dilution of the original inoculum of infected cells prevented renewed viral growth after U-90152 was removed at day 24. The combination of U-90152 and AZT, each at 0.5 μM, also totally prevented viral spread. Finally, although the RT amino acid substitutions K103N (lysine **103** to asparagine) and Y181C (tyrosine 181 to cysteine), which confer cross-resistance to several nonnucleoside inhibitors, also decrease the potency of U-90152, this drug retains significant activity against these mutant RTs in vitro (IC50s, approx. 8 μM).

L12 ANSWER 43 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:400359 CAPLUS
DN 119:359
TI Sulfonic acid polymers are potent inhibitors of HIV-1 induced cytopathogenicity and the reverse transcriptases of both HIV-1 and HIV-2
AU Tan, Ghee T.; Wickramasinghe, Anura; Verma, Sandeep; Hughes, Stephen H.; Pezzuto, John M.; Baba, Masanori; Mohan, Prem
CS Program for Collaborative Research in the Pharmaceutical Sciences, University of Illinois at, Chicago, IL, USA
SO Biochimica et Biophysica Acta (1993), 1181(2), 183-8
CODEN: BBACAQ; ISSN: 0006-3002
DT Journal
LA English
AB Four novel sulfonic acid polymers were evaluated for their in vitro HIV-1 and **HIV**-2 **reverse transcriptase** (RT) inhibitory activity and found to be equipotent against both RTs. The aromatic polymers demonstrated IC50 values that were approx. **103**-fold lower than those observed with the aliphatic polymers. Among the aromatic polymers, poly(4-styrenesulfonic acid) (PSS) (MW 8000; IC50 = 0.02 μg/mL) was 3-fold more potent than poly(anetholesulfonic acid) (PAS) of approx. the same mol. weight range. The activity of PSS polymers increased in proportion to the size of the polymers and, relative to suramin, activity could be enhanced over 200-fold. These polymers also inhibited the cytopathic effect of HIV-1 at concns. that were non-toxic to MT-4 cells. The potent RT inhibitory properties of these stable sulfonic acid polymers suggest that structure-activity studies are warranted to yield agents capable of inhibiting multiple stages of the viral process.

L12 ANSWER 44 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:32541 CAPLUS
DN 118:32541
TI **HIV**-1 specific **reverse transcriptase** inhibitors show differential activity against HIV-1 mutant strains containing different amino acid substitutions in the reverse transcriptase
AU Balzarini, Jan; Karlsson, Ana; Perez-Perez, Maria Jesus; Vrang, Lotta; Walbers, Johan; Zhang, Hong; Oeberg, Bo; Vandamme, Anne Mieke; Camarasa, Maria Jose; De Clercq, Erik
CS Rega Inst. Med. Res., KU Leuven, Louvain, B-3000, Belg.
SO Virology (1992), 192(1), 246-53
CODEN: VIRLAX; ISSN: 0042-6822
DT Journal
LA English
AB Serial passage of HIV-1 in CEM or MT-4 cell cultures in the presence of different **HIV**-1 specific **reverse transcriptase** (RT) inhibitors yielded mutant viruses which were resistant, i.e.,

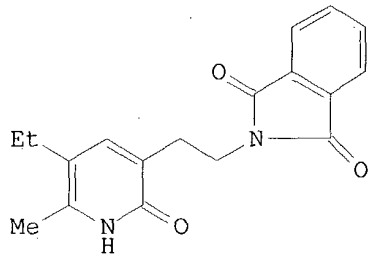
200-1000-fold less sensitive, to the homologous compds. The RT of these mutant HIV-1 strains showed different amino acid substitutions depending on the class of the HIV-1-specific RT inhibitors. The following amino acid substitutions were found: 138 Glu → Lys (TSAO-T), 181 Tyr → Cys (nevirapine), 181 Tyr → Cys (pyridinone), and 100 Leu → Ile (TIBO R82150). Four TIBO (R82913)-resistant HIV-1 strains contained different amino acid substitutions: **103** Lys → Asn (strain 2), 100 Leu → Ile and 138 Glu → Lys (strain B02), 100 Leu → Ile and 181 Tyr → Cys (strain 1), 100 Leu → Ile and 188 Tyr → His (strain B22). The level of cross-resistance (or sensitivity) highly depends on the nature of the amino acid substitutions. As a rule, the TSAO-resistant HIV-1 strains (138 Glu → Lys) and TIBO (r82150 or R82913)-resistant HIV-1 strains (Leu 100 → Ile or **103** Lys → Asn) are sensitive to the other HIV-1-specific RT inhibitors, whereas the amino acid change 181 Tyr → Cys results in a significant reduction of sensitivity to all classes of the HIV-1 specific RT inhibitors.

L12 ANSWER 45 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:527285 CAPLUS
DN 117:127285
TI Functional analysis of **HIV**-1 **reverse transcriptase** amino acids involved in resistance to multiple nonnucleoside inhibitors
AU Sardana, Vinod V.; Emini, Emilio A.; Gotlib, Leah; Graham, Donald J.; Lineberger, Donald W.; Long, William J.; Schlabach, Abner J.; Wolfgang, Jill A.; Condra, Jon H.
CS Dep. Virus Cell Biol., Merck Sharp and Dohme Res. Lab., West Point, PA, 19486-0004, USA
SO Journal of Biological Chemistry (1992), 267(25), 17526-30
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Several novel, structurally distinct classes of specific human immunodeficiency virus type 1 (**HIV**-1) **reverse transcriptase** (RT) nonnucleoside inhibitors have been described recently. These include the pyridinone derivs. L-697,639; L-697,661; and L-696,229 as well as BI-RG-587 and the tetrahydroimidazo[4,5,1-j,k]-benzodiazepin-2(1H)-one and -thione compds. Previous studies have implicated involvement of the RT amino acid residues at positions **103**, 181, and 188 in the activity of the compds. Accordingly, HIV-1 RT mutants containing a series of amino acid substitutions at these positions were constructed. The relative resistance of purified mutant enzymes to each of the inhibitors was assessed. This anal. established the functional equivalence of the three inhibitor classes and provided evidence for the interaction of the **103** site with the 181/188 region. Amino acid substitutions at these positions were also found to influence RT sensitivity to inhibition by phosphonoformate, thereby suggesting a close association between this pyrophosphate analog's binding site in RT and the binding site of the nonnucleoside inhibitors. In addition, aromatic stacking of the amino acid side groups at residues 181 and 188 was suggested to be required for inhibitor activity.

L12 ANSWER 46 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:527283 CAPLUS
DN 117:127283
TI Conformational changes of **HIV reverse transcriptase** subunits on formation of the heterodimer. Correlation with kcat and Km
AU Anderson, Stephen F.; Coleman, Joseph E.
CS Dep. Mol. Biophys. Biochem., Yale Univ., New Haven, CT, 06510, USA
SO Biochemistry (1992), 31(35), 8221-8
CODEN: BICHAW; ISSN: 0006-2960
DT Journal

LA English
AB Reverse transcriptase (RT) from human immunodeficiency virus (HIV) is initially expressed as a 66-kDa protein and is subsequently proteolytically processed in vivo to form a 66-kDa/51-kDa heterodimer. Comparison of CD spectra of the 66-kDa, 51-kDa, and heterodimeric forms of RT indicated that the conversion was accompanied by dramatic changes in subunit conformation. The mean residue ellipticity per subunit at 220 nm decreased from -10.7 + **103** deg cm2 dmol-1 for the 66-kDa protein to -6 + **103** deg cm2 dmol-1 for the heterodimer. The same loss of ellipticity was observed whether the heterodimer was produced by proteolysis or by mixing a sep. expressed cloned 51-kDa subunit with the 66-kDa protein. Comparison with the spectrum of the cloned 51-kDa protein suggested that much of the conformational change arises from the formation of the 51-kDa subunit, but substantial changes occur in the remaining 66-kDa subunit as well. A kinetic anal. was performed to correlate these conformational changes with changes in enzyme function. Application of an integrated Michaelis-Menten equation to the catalysis of poly(dT) formation using d(pT)20-poly(rA) primer-template showed that the kcat for the heterodimer is approx. half that of the 66-kDa enzyme, decreasing from 2.9 to 1.2 nucleotides/s upon formation of the heterodimer. However, the Km values for the primer-template decreased from 0.54 to 0.12 μM upon heterodimer formation. Thus, the kcat/Km was 2-fold larger for the heterodimer, giving it a distinct catalytic advantage at undersatg. concns. of enzyme and primer-template. These kinetic data were compatible with a model in which half the polymerase active centers are inactivated on formation of the heterodimer, but this loss of catalytic potential is more than offset by an increase in affinity of the heterodimer for the primer-template.

L12 ANSWER 47 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:524045 CAPLUS
DN 117:124045
TI Viral resistance to human immunodeficiency virus type 1-specific pyridinone reverse transcriptase inhibitors
AU Nunberg, Jack H.; Schleif, William A.; Boots, Evelyn J.; O'Brien, Julie A.; Quintero, Julio C.; Hoffman, Jacob M.; Emini, Emilio A.; Goldman, Mark E.
CS Dep. Virus Cell Biol., Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SO Journal of Virology (1991), 65(9), 4887-92
CODEN: JOVIAM; ISSN: 0022-538X
DT Journal
LA English
GI



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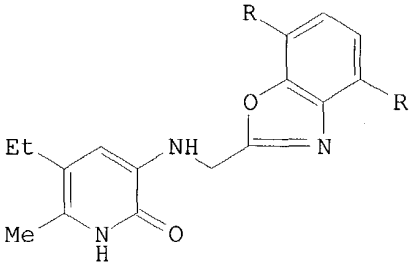


II, R=H

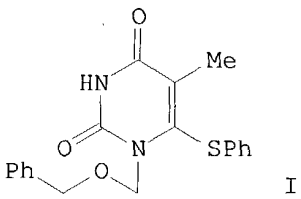
III, R=Me

AB Human immunodeficiency virus type 1 (**HIV**-1)-specific pyridinone **reverse transcriptase** (RT) inhibitors (I-III) prevent HIV-1 replication in cell culture. In contrast to nucleoside analog inhibitors, such as AZT, which need to be converted to triphosphates by host cells, these compds. act directly to inhibit RT via a mechanism which is noncompetitive with respect to deoxynucleoside triphosphates. As one approach to define the mechanism of action of pyridinone inhibitors, the authors isolated resistant mutants of HIV-1 in cell culture. Serial passage in the presence of inhibitor yielded virus which was 1,000-fold resistant to compds. of this class. Bacterially expressed RTs molecularly cloned from resistant viruses were also resistant. The resistant RT genes encoded two amino acid changes, K-**103** to N and Y-181 to C, each of which contributed partial resistance. The mutation at amino acid **103** lies within a region of RT which may be involved in PP1 binding. The resistant viruses, although sensitive to nucleoside analogs, were cross-resistant to the structurally unrelated RT inhibitors TIBO R82150. Thus, these nonnucleoside analog inhibitors may share a common binding site on RT and may all make up a single pharmacol. class of RT inhibitor. This observation may have important implications for the clin. development of these compds.

L12 ANSWER 48 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1991:467189 CAPLUS
DN 115:67189
TI Polymerase and immunological activities of the **HIV**-I viral recombinant **reverse transcriptase** isolated from Escherichia coli
AU Shvetsov, Yu. P.; Mel'nikov, A. A.; Suvorova, Z. K.; Kopylova-Sviridova, T. N.; Pokrovskii, V. V.; Fodor, I. I.
CS Inst. Biokhim. Fizoiol. Mikroorg. Inst., USSR
SO Molekulyarnaya Genetika, Mikrobiologiya i Virusologiya (1991), (3), 22-4
CODEN: MGMVDU; ISSN: 0208-0613
DT Journal
LA Russian
AB The recombinant reverse transcriptase of HIV-1 virus was isolated from E. coli cells transformed by the plasmid pRT40 DNA. The **103** kD protein produced by these cells is processed to proteins with lower mol. masses by the reverse transcriptase precursor-specific viral protease as well as by E. coli proteases. The resulting **103**-66 kD proteins possess the polymerase activity while 51 Kd and smaller proteins lack the activity. The 66 and 51 kD reverse transcriptase fragments demonstrate

pos. immunol. reaction with human blood serum from the people possessing antibodies to HIV-1 virus. The recombinant reverse transcriptase of HIV-1 produced by E. coli cells is shown to be useful in AIDS diagnosis in humans.

L12 ANSWER 49 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1991:199140 CAPLUS
DN 114:199140
TI Potent and selective inhibition of human immunodeficiency virus type 1 (HIV-1) by 5-ethyl-6-phenylthiouracil derivatives through their interaction with the **HIV-1 reverse transcriptase**
AU Baba, Masanori; De Clercq, Erik; Tanaka, Hiromichi; Ubasawa, Masaru; Takashima, Hideaki; Sekiya, Kouichi; Nitta, Issei; Umezu, Kohei; Nakashima, Hideki; et al.
CS Dep. Bacteriol., Fukushima Med. Coll., Fukushima, 960-12, Japan
SO Proceedings of the National Academy of Sciences of the United States of America (1991), 88(6), 2356-60
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
GI



I

AB Several 5-ethyl-6-(phenylthio)uracil analogs with potent and selective activity against human immunodeficiency virus (HIV) type 1 are described. 1-Benzyloxymethyl-5-ethyl-6-phenylthiouracil (I), the most potent congener of the series, inhibits HIV-1 replication in a variety of cell systems, including peripheral blood lymphocytes, at a concentration of 1.5-7.0 nM, which is lower by a factor of **103** than the 50% antivirally effective concentration of the parent compound 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT). The 5-ethyl-6-(phenylthio)uracil analogs, like HEPT itself, do not inhibit HIV-2 replication but do inhibit replication of 3'-azido-3'-deoxythymidine-resistant mutants of HIV-1. 1-Benzyloxymethyl-5-ethyl-6-phenylthiouracil and its congeners are targeted at the **HIV-1 reverse transcriptase** (RT). They do not inhibit HIV-2 RT. They do not need to be metabolized to exert their inhibitory effect on HIV-1 RT. Yet this inhibitory effect is competitive with the natural substrate dTTP. The HEPT derivs. represent a group of RT inhibitors with a unique mode of interaction with HIV-1 RT.